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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
*10/018,222	12/18/2001	Tsutomu Kakuyama	Q67737	7906

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EXAMINER
PATTEN, PATRICIA A

ART UNIT	PAPER NUMBER
1654	7

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,222	KAKUYAMA, TSUTOMU	
	Examiner	Art Unit	
	Patricia A Patten	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 13-23 are pending in the application.

Election/Restrictions

Applicant's election of Group III in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 13-23 were examined on the merits with regard to the elected species of cysteine.

Priority

The Specification lacks the necessary reference to the prior PCT application and the foreign priority document. It is asked that Applicant insert, immediately after the title, a statement which reads: "This application is a 371 of PCT/JP00/04440 filed on 07/03/2000 which claims benefit of priority to Application No. 11/188132 filed in Japan on 07/01/09."

Specification

A substitute specification in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) is required. The substitute specification filed must be accompanied by a statement that it contains no new matter. Although the Specification is not illegible, there are numerous grammatical and spelling errors. For example, the term 'heme' is misspelled throughout the Specification as 'hem'. Further, line 1 of the Specification reads 'Hemoglobin is a hem-protein existed in red blood cell' which should properly read: 'Hemoglobin is a heme-protein existing in red blood cells'. Please note that there are too numerous grammatical errors for the Examiner to point out.

Abstract of the Disclosure

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The

abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

In the Instant case, the Abstract recites 'said stabilizing agent' (legal phraseology). Additionally, the Abstract begins by reciting 'The present invention *resides in* a stabilizing agent...' (Emphasis added). The phrase 'resides in' is not considered clear and concise language. It is asked that Applicant submit a new Abstract which does not contain legal phraseology, and which describes the invention more concisely; i.e., 'A composition and method for stabilizing hemoglobin by....'.

Claim Objections

Claims 15 and 16 are objected to because of the following informalities: Claim 15 recites 'sulfur-containing' while the rest of the claims recite 'sulfur containing'. It is suggested that Applicant amends 'sulfur-containing' to 'sulfur containing' in order to remain consistent throughout the claims. Both claims 15 and 16 recite 'SH' group. In order to conform to proper chemical nomenclature, it is suggested that 'SH' be changed

to 'thiol'. Further, both of these claims recite 'having SH group' which is missing the definite article 'a' or 'an'. This is a minor grammatical error; 'compound is a sulfur containing compound having a thiol group' is a suggestion for rewording the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17 and 18 recite 'or a compound and the family thereof'. This phrase is confusing in that it is not known what compound the claim is referring to. Further, 'the family thereof' is indefinite in that it is not clear what family the claim means, and this term appears to lack antecedent basis in their respective claims as well as the independent claim. Is this a family of sulfur containing compounds? It appears that Applicant may mean 'or a compound *in* the family thereof' as claimed in claims 19 and

20 but the Examiner is unsure. However, even if the 'and' in this phrase were changed to 'in', it remains unclear what 'family' the claim is referring to. It is suggested that applicants clearly point out what family the claim is referring to.

As stated *supra,* Claims 19 and 20 recite 'or a compound in the family thereof.' Again, it is unclear what the term 'the family' refers to, and this term further appears to lack antecedent basis in their respective claims as well as the independent claim. Therefore, claims 19 and 20 are also indefinite.

Claims 21 and 22 are indefinite in that it is unclear exactly how Applicant intends to limit the broad claim 13. Specifically, the phrase which reads 'wherein sulfur is added in an amount of 0.1 to 0.0001 parts by weight per one part by weight of hemoglobin' is indefinite. It is noted that claim 21 is a composition claim, rather than a method claim. Therefore, the functional language in the claim would confuse the ordinary artisan: is the sulfur present in the composition in this range? Further, the term 'said sulfur' lacks antecedent basis in the claims because the claims previously stated 'sulfur containing compounds'. Further, Claims 21 and 22 recite 0.1 to 0.0001 parts by weight ...'. It is unclear if this means parts by weight of hemoglobin, or parts by weight of the entire solution. Because the Examiner cannot determine exactly what Applicants mean by this phrase, the claims were not examined further with regard to applying prior art.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-22 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Light et al. (US 5,895,810).

Light et al. (US 5,895,810) acknowledged the need for hemoglobin which resisted degradation and methemoglobin production (methemoglobin is the oxidized form of iron, Fe (III) which will not bind oxygen and therefore is unusable as a blood substitute) as a blood substitute for treating blood loss occurring from anemia or hemorrhage (col.1, lines 16-21 and 55-63). Light et al. thus disclosed a method for

stabilizing hemoglobin with sulfhydryl compounds including D, L-cysteine (aka, cysteine) via deoxygenating hemoglobin, gas exchange with an inert gas and chemical scavenging with reducing agents such as cysteine (col.3, lines 59-65 and col.4, lines 28-35). Cysteine is well known in the art as a sulfur containing amino acid (contains an 'SH'/thiol group).

Light et al. specifically claimed a method for preparing a hemoglobin solution via mixing deoxygenated hemoglobin with a sulfhydryl compound such as D,L-cysteine (Claim 1). Therefore, the composition produced by the method was known, and anticipated by Light et al. because practicing the method would have necessarily produced the composition: When the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter 1990).

Alternatively, the ordinary artisan would have been motivated to have added cysteine to a solution containing hemoglobin, because Light et al. specifically taught that when the method incorporated cysteine, it produced a stable blood substitute (Claim 1, col. 4, lines 22-35). Thus, the ordinary artisan would have had a reasonable expectation that the incorporation of cysteine into a solution containing deoxy-Hb would have successfully stabilized the deoxy-Hb thereby creating a blood substitute with improved stability.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Light et al. (US 5,895,810) in light of Fiechtner et al. (US 5,686,316)* and in light of Stark (US 6,124,134)*. Claims 23-24 are drawn to wherein the hemoglobin is glycated hemoglobin.

The teachings of Light et al. were discussed *supra*. Light et al. did not specifically teach wherein the hemoglobin was glycated.

Fiechtner et al. (US 5,686,316) taught that "The human erythrocyte is freely permeable to glucose. Within each erythrocyte, glycated hemoglobin is formed from hemoglobin A (the native, normal form) at a rate proportional to the ambient glucose concentration....a fraction of the hemoglobin is modified during the life span of the erythrocyte (120 days) and is irreversible." (col.1, lines 18-29). "Glycated hemoglobin is present in non-diabetics at a level of about 5%..." (col.1, lines 31-34).

Stark (US 6,124,134) taught that "HbA_{1c} consists of 50 to 90% hemoglobin glycated by a ketoamine linkage at the beta chain N-terminal valine residue" (col.1, lines 35-37). HbA_{1c} is glycated hemoglobin.

One of ordinary skill in the art would have been motivated to prepare a solution containing a glycated hemoglobin with cysteine because one would have had a reasonable expectation that cysteine would have suitably stabilized glycated hemoglobin. According to Fiechtner et al., at any given moment, some hemoglobin in erythrocytes is glycated. Thus, the ordinary artisan would have had a reasonable expectation that at least some of the hemoglobin purified by Light et al. for incorporation into a stabilized hemoglobin solution with cysteine, was glycated.

Further, the ordinary artisan would have easily recognized that stabilization of the hemoglobin via a sulfhydryl moiety (i.e., cysteine or N-acetyl-L-cysteine for example) would have reduced the iron on the heme ring (each of four subunits in the hemoglobin tetramer protein contains a ferroprotoporphyrin IX which reversibly binds oxygen and molecules such as CO_2, and according to Light et al., thiol moieties such as cysteine) regardless of the presence of an attached glucose molecule. This would be clear to the ordinary artisan since glucose does not bind to the heme molecule, but bonds to an amino acid found in the protein portion of the hemoglobin as evidenced by Stark (*supra*). Accordingly, Applicant has indicated in the Specification that '..a term of hemoglobin is used, as totally including hemoglobin and glycated hemoglobin'. This is

interpreted by the Examiner to mean that Applicant recognizes that purified hemoglobin will include some glycated hemoglobin, and that the procedure for stabilizing either hemoglobin A (more abundantly found) or hemoglobin A_1 (glycated hemoglobin) is analogous.

* These references have been cited merely to relay intrinsic properties of hemoglobin and glycated hemoglobin, and are not being used in the rejection *per se*.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Patricia Patten, whose telephone number is (703)308-1189. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback is on 703-306-3220 The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.